R E M A R K S

It is believed that this application has been amended in a manner that places it in condition for allowance at the time of the next Official Action.

In the outstanding Official Action, the specification was objected to for allegedly not being in compliance with the requirements for patent applications containing nucleotide and/or amino acid sequences. It is believed that the present amendment obviates this objection.

The text on page 5, last paragraph and page 7, third paragraph have been amended so that the sequence identification numbers appear as SEQ ID NO:X, wherein "X" is the sequence number. Thus, it is believed that the present disclosure complies with the requirements for applications containing nucleotide sequences and/or amino acid sequences.

The outstanding Official Action also objected to the specification for not referring to the benefits of the earlier provisional application No. 60/217,098. The present specification has been amended on page 1 to indicate that the present application claims priority to Unites States provisional application No. 60/217,098. Thus, it is believed that the present disclosure complies with the requirements of 37 CFR §1.78.

In the outstanding Official Action, the oath or declaration was found defective. The outstanding Official Action

stated that the oath or declaration did not identify the citizenship of inventor Lannfelt. This contention is respectfully traversed.

The Examiner's attention is respectfully directed to the Combined Declaration for Patent Application and Power of Attorney filed on February 28, 2002. Applicant respectfully submits that the declaration clearly states that the citizenship of inventor Lannfelt is Swedish. Thus, it is believed that the declaration is proper. A copy for the Examiner's convenience is enclosed with this amendment.

Beginning on page 3, the outstanding Official Action alleged that the figures of the present application did not comply with 37 CFR §1.84(u)(1). The Official Action stated that when partial views of a drawing are intended to form one complete view, the figure must be identified by the same number followed by a capital letter. Applicant notes this contention and respectfully requests that the corrections to the drawings be held in abeyance until the present application is in condition for allowance.

The outstanding Official Action noted the use of trademarks in the present application. Accordingly, the present specification has been amended so that trademarks referred to on pages 12 and 13 have been capitalized. As to incorporating generic terminology that describes the trademarks, applicant believes that the terms "cite-directed mutogenisis kit" and

"transfection reagent" already adequately describe the nature of the marks. Thus, it is believed that the present specification complies with the requirements for incorporating trademarks in a patent application.

Claims 18 and 19 were objected to for containing the term "immunosation". It is believed that the present amendment obviates this objection. Claims 17-23 have been canceled and new claims 24-38 have been added. Claims 24-38 recite the preferred spelling "immunization".

In the outstanding Official Action, claims 17-23 were rejected under 35 USC §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As noted above, claims 17-23 have been canceled. New claims 24-38 have been added. It is believed to be apparent that claims 24-38 have been drafted in a manner so as to obviate the contention that the claims of the present invention are indefinite.

Claims 17, 18 and 22 were rejected under 35 USC §102(b) as allegedly being anticipated by KLINE et al. In light of the present amendment, this rejection is respectfully traversed.

It is respectfully submitted that the cited publications in the outstanding Official Action fail to disclose or suggest the claimed invention. Claims 24-28 focus on the use

of non-wildtype Aβ protofibrils for the prevention or treatment of Alzheimer's disease. There are several important differences between an Aβ protofibrils, Aβ peptides and Aβ fibrils, which are distinct Aβ forms.

It is believed that each form exhibits a different conformation and biological profile. Moreover, each form exhibits a distinct solubility and molecular weight. Protofibrils, for example, are soluble whereas fibrils are insoluble. The molecular weight of an Aβ peptide is approximately 4,500 daltons. The molecular weight of an Aβ protofibril is in the range of 100,000-500,000 daltons. Fibrils have even higher molecular weights. Structurally, protofibrils and fibrils are mainly in a β sheet conformation. However, an Aβ peptide is mainly α-helical. Thus, it is believed that each Aβ form is a unique chemical entity.

It is respectfully submitted that KLINE et al. fail to disclose or suggest the claimed protofibrils. While KLINE et al. refer to neurofilaments containing amyloid β protein constructs, KLINE et al. make no reference to protofibrils or fibrils. Thus, it is believed that KLINE et al. fail to contemplate an Aβ protofibril that has a molecular weight in a range of 100,000-500,000 daltons or a β sheet conformation.

KLINE et al. broadly teach that amyloid beta proteins may be used to treat Alzheimer's disease, the claimed invention relates to the use of non-wild type protofibrils in combination

with an Arctic mutation to treat Alzheimer's disease. The Arctic mutation confers a distinct and unique property to Aβ peptides in that they will form considerably more stable Protofibrils than wild type Aβ peptides. Hence, Aβ peptides with the Arctic mutation offer for the first time the capability of preparing a vaccine antigen or a monoclonal antibody that targets protofibrils rather than amyloid fibril plaques.

Since, protofibrils are likely to be pathogens initiating a disease process before the formation of amyloid plaques has occurred, the invention provides for the early treatment and prevention of Alzheimer's disease. There is no teaching in WO95/31996 as to what Aβ form should be used for treatment or prevention of Alzheimer's disease. Moreover, there is no teaching as to the use of non wild type protofibrils. Thus, Applicants believe that it cannot be said that KLINE et al. anticipates r renders obvious the claimed invention.

Claims 17, 18, 19, 22 and 23 were rejected under 35 USC §102(b) as allegedly being anticipated by SCHENK. This rejection is respectfully traversed.

The outstanding Official Action alleged that SCHENK discloses a method of preventing or treating Alzheimer's disease by administration of an agent capable of inducing an immune response against a peptide component of an amyloid deposit in a patient. However, Applicant respectfully submits that the SCHENK publication describes a method for the preparation of "aggregated

Aβ peptides" (WO 99/27944, page 50, lines 6-35). According to this method, insoluble fibrils are formed that are distinct from protofibrils. In particular, the solubility of the fibrils are different. The SCHENK publication is directed to insoluble Aβ fibrils. In fact, the Examiner's attention is respectfully directed to page 50, lines 7-20, wherein it is provided that the SCHENK publication is directed to insoluble (precipitated) Aβ fibrils.

Thus, while SCHENK may teach the use of amyloid beta peptide (Aβ) to treat Alzheimer's disease, the vaccine disclosed by SCHENK utilizes aggregated forms (fibrils) of wild type Aβ peptides as antigens. They are capable of generating an immune response against fibrils (a component of amyloid plaques) in the brain of a patient suffering from Alzheimer's disease. As SCHENK et al. fail to disclose or even suggest stable protofibrils, it is believed that SCHENK et al. fail to anticipate or render obvious the claimed invention.

In view of the present amendment and the foregoing remarks, therefore, it is believed that this application is now in condition for allowance, with claims 24-38 as presented. Allowance and passage to issue on that basis are accordingly respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Page 5, the last full paragraph has been replaced as follows:

--The Aβ-Arc as disclosed in [SEQ ID NO 1] SEQ ID NO: 1. Aβ-Arc comprises 39, 40 or 42 amino acids but may also be shorter as long as the protofibril forming ability is maintained.--

Page 7, the third full paragraph has been replaced as follows:

--In yet a further aspect, the invention relates to antibodies against the Aβ peptide of [SEQ ID NO 1] SEQ ID NO: 1. The antibodies may be monoclonal or polyclonal or antibody fragments. Preferably the antibodies are humanized for use in passive immunisation for prevention of therapy against AD. Thus, antibodies which react with the unique epitope created by glycine at condon 693 are provided.--

Page 12, the last full paragraph, bridging page 13, has been replaced as follows:

--The effect of the Arctic mutation on Aβ formation was further investigated *in vitro* in transiently transfected HEK293 cells. APPwt was compared to the following mutations: Arctic (APP_{E693G}), Dutch (APP_{E693Q}), Italian (APP_{E693K}) and Flemish (APP_{A692G}). Constructs containing the Swedish double mutation (APP_{Swe}) and one APP mutation at codon 717 (APP_{V717F}), both with well-studied APP

processing characteristics (Hardy (1997)), were used as positive controls. The mutations were introduced to APP695 cDNA in pcDNA3 using [QuikChange™] QUICKCHANGE™ Site-Directed Mutagenesis Kit according to the manufacturers instructions (Stratagene). The mutated constructs were verified by sequencing. For the ELISA measurements, HEK293 cells were seeded in six-well dishes and transfected with the different constructs using [FuGENE™] FUGENE™ 6 Transfection Reagent (Roche Diagnostics) according to the manufacturers instructions. 24 h after transfection, the cells were conditioned 48 h in OptiMEM containing 5% newborn calf serum. After withdrawal of the media for ELISA measurements, the APP expression in the cells were investigated by western blot using monoclonal antibody 22C11 (Roche Diagnostics). Media was conditioned and analyzed for Aβ levels by the same Aβ42- and Aβ40-specific sandwich ELISA systems as used for human plasma (Citron, et al. (1997)). The Aβ42 and Aβ40 concentrations and Aβ42/40 ratios are shown in Table 1.--